Medical and Pediatric Oncology 29:73–78 (1997)

Foreword

Central nervous system (CNS) manifestations of Langerhans cell histiocytosis (LCH) remain among the major enigmas of this puzzling disease. The Histiocyte Society therefore covened a workshop on CNS LCH at the time of its 1996 meeting in Vienna, Austria. Prof. H. Gadner and Dr. N. Grois undertook this formidable assignment, and gathered an outstanding faculty to address the issues. A thorough review of the pathology, diagnostic tests, pathophysiology, available therapies and directions for future clinical and laboratory research was the result, and is summarized in the report that appears below.

Of particular interest in the report is the proposed systematization of CNS disease as visualized by modern magnetic resonance imaging techniques. The system, which is described in detail, is based on 38 LCH children with CNS lesions—a relatively large number—available to the investigators for review and analysis.

Another important point brought out in the report concerns a possible mechanism to explain the otherwise inexplicable, inexorable parenchymal disorders sometimes seen in LCH patients. The authors call attention to the pathogenesis of the progressive dementia seen in such diseases as HIV infection. This is associated with inappropriate activation of glutamate receptors and neuronal cell damage and death. Since CNS LCH of this type is rare in children, those with the syndrome might well be enrolled in current clinical studies of adults with similar processes. This seems a potentially fruitful area of research, since it might not only help in the understanding of the pathophysiology of CNS LCH, but also open pathways to effective therapy. Both are badly neded.

It can be seen from the foregoing and what follows that the goals of the Histiocyte Society were amply met in Vienna in 1996, and that Prof. H. Gadner and Dr. N. Grois fully merited the thanks and the congratulations extended to them at that time for the excellent and illuminating meeting they organized.

Giulio J. D'Angio, M.D.
Editor-in-Chief

Report of the Histiocyte Society Workshop on "Central Nervous System (CNS) Disease in Langerhans Cell Histiocytosis (LCH)"

Held at the
XIIth Histiocyte Society Annual Meeting
Juridicum, University of Jurisprudence Vienna,
Vienna, Austria
September 19, 1996

PARTICIPANTS

G. Bernert, MD	Department of Pediatric Neuropsychiatry, University of Vienna, Vienna, Austria
V. Broadbent, MD	Cambridge Health Authority, Addenbrookes Hospital Paediatric Department, Cambridge, U.K.
T. Czech, MD	Department of Neurosurgery, University of Vienna, Vienna, Austria
G. D'Angio, MD	Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia
M. Egeler, MD	Section Hematology-Oncology, Sophia Kinderziekenhuis, Rotterdam, The Netherlands
B.E. Favara, MD	Department of Health and Human Services, Rocky Mountain Laboratories, Hamilton, Montana
N. Grois, MD	St. Anna Children's Hospital, Vienna, Austria

© 1997 Wiley-Liss, Inc.

G. Kannourakis, MD	Ballarat Cancer Research Centre, University of Ballarat, St. John of God Hospital, Ballarat, Victoria, Australia
J. Kepes MD, FRSM	Department of Pathology and Laboratory Medicine, University of Kansas City Medical Center, Kansas City
G.H. Mostbeck, MD	Department of Radiology, University of Vienna, Vienna, Austria
D. Prayer, MD	Department of Neuroradiology, University of Vienna, Vienna, Austria

The aims of this workshop were 1) to increase the awareness of CNS disease associated with LCH, 2) to describe the various clinical presentations, the imaging findings, and the histopathology, 3) to formulate guidelines for the diagnostic and therapeutic management of affected patients, and 4) to stimulate research efforts to further elucidate the pathogenesis of the disorder.

The program follows:

Part I. WHAT IS KNOWN TO DATE?
(Moderator: G. D'Angio)

1. Historical review (J. Kepes)
2. Clinical spectrum (N. Grois)
3. Imaging findings (G.H. Mostbeck, D. Prayer)
4. Histopathology (B.E. Favara)
5. Therapy, outcome and long-term consequences (N. Grois)
6. Illustrative presentations
   - J. Pritchard, V. Yanuri:
     Neurological disease in a boy with congenital multisystem LCH.
   - J. Goldberg:
     Primary Langerhans cell histicytosis of the parieto-occipital lobe.
   - M. Maghnie:
     Are dynamic endocrine tests useful in predicting hormone deficiency during childhood LCH?
   - B.E. Favara:
     Dendritic histiocytosis of the central nervous system.

Part II. WHAT ARE THE OPEN QUESTIONS? WHAT ARE THE FUTURE SUGGESTIONS?
(Moderator: N. Grois)

Consensus concerning future studies
- V. Broadbent:
  Screening tests, diagnostic evaluation and follow up programs.
- G. Bernert:
  Neuropsychiatric evaluation, follow-up and screening.
- G.H. Mostbeck, D. Prayer:
  Appropriate imaging methods.
- T. Czech:
  Role of brain biopsy, role of neurosurgery—risks and indications.
- G. D'Angio:
  Role of radiotherapy—risks and benefits.
- M. Egeler:
  Role of chemotherapy, immunotherapy, experimental therapeutic approaches.
- G. Kannourakis:
  Cytokine studies on CSF or tissue.
- J. Kepes, B.E. Favara:
  Processing of brain tissue and CSF specimen.
- B.E. Favara:
  Research thrusts.

• Summation and discussion

SUMMARY AND RECOMMENDATIONS

I. What is Known to Date?

Reviews of the literature and a retrospective collection of 38 cases by one of the authors (N.G.) show that all parts of the CNS can be involved by LC, in all age groups [1,2]. The majority of the patients have multiple organ involvement of LCH, often with lesions in the skull, orbits or the mastoid region. The commonest sites of CNS involvement were, in order of frequency, the hypothalamic-pituitary region, the cerebellum, pons, and cerebral hemispheres. However, lesions in the basal ganglia, spinal cord, the optic nerves and tract have also been observed.

Symptoms of CNS involvement could occur years before but more often years after the initial diagnosis of LCH and were dependent on the site and type of lesions. In the hypothalamic-pituitary region endocrine deficiencies ranging from diabetes insipidus to panhypopituiarism and behavioural disturbances were seen, sometimes heralding the involvement of other parts of the brain.

Extraaxial lesions deriving from the dura, meninges or choroid plexus exerting a mass effect led to symptoms of raised intracranial pressure, focal symptoms or to hydrocephalus. These lesions often occurred many years after the initial diagnosis of LCH and could be surgically removed in most instances or responded well to additional treatment with steroids and/or chemotherapy.

Lesions in the cerebellum or pons often concurred or

were associated with other CNS lesions, extraparenchymal or in the hypothalamic-pituitary region. Neurologic symptoms ranged from discrete intellectual and behavioural changes or subtle hypo- or hyperreflexia to severe ataxia, tremor, dysarthria, eventually leading to fatal CNS degeneration despite various treatment approaches and independent from the course of LCH outside the CNS.

Magnetic Resonance Imaging of LCH-CNS Lesions

MR imaging is currently the technique of choice for demonstrating lesions in the CNS. Based on a retrospective collection of the imaging material from 38 patients with LCH and CNS disease the broad spectrum of parenchymal and extraparenchymal CNS lesions seen in such patients was summarized. More than one type of lesion was commonly found in a given patient. Many of the pathologic changes found by MR imaging are per se not specific for LCH, but the characteristic distribution, MR morphology and contrast enhancement pattern suggest the correct diagnosis in the appropriate clinical setting. The following classification system was proposed to describe the spectrum of lesions seen in LCH-CNS patients.

- *Type I.a. White matter lesions without enhancement* (21/38 patients, 55%). These lesions were predominantly located in the pons, the cerebellar peduncles and the cerebellar white matter. They presented as poorly-defined areas of low signal-intensity on T1-weighted images and high signal-intensity on T2-weighted and proton-density weighted images. Multiple sclerosis, acute disseminated encephalomyelitis (ADEM), leucodystrophies, and infections have to be considered among the possible diagnoses.
- *Type I.b. White matter lesions with enhancement* (9/38 patients, 24%) As with type I.a. there was a striking infratentorial location. The lesions presented as poorly to well-defined areas of prolonged T1 and T2 relaxation times i.e. low signal-intensity on T1-weighted images and high signal-intensity on T2-weighted and proton-density weighted images, without a mass effect and strong Gd-DTPA enhancement (blood-brain-barrier breakdown). The differential diagnosis includes multiple sclerosis, ADEM, metastases, and sarcoidosis.
- *Type II.a. Gray matter lesions without enhancement* (19/38 patients, 50%) Changes of this type were mostly seen in the dentate nucleus with bilateral involvement as areas of low signal intensity on T1-weighted images and high signal intensity on T2-weighted and proton-density weighted images. These lesions showed no mass effect, sometimes, however, calcification was present and must be distinguished from Fahr disease (if calcified), ADEM, glioma, or, infarction.
- *Type II.b. Gray matter lesions with enhancement* (3/38 patients, 8%) were predominantly located in the cerebellar gray matter and basal ganglia. Well-defined areas of low signal-intensity on T1-weighted images and high signal-intensity on T2-weighted and proton-density weighted images showed a mass effect and strong Gd-DTPA enhancement and were sometimes surrounded by edema. Such lesions can be mistaken for neoplasms like ganglioglioma.
- *Type III. Extraparenchymal lesions* These masses were **a:** dural based (12/38 patients, 32%), **b:** arachnoid based (2/38 patients, 5%) or **c:** choroid plexus based (3/38 patients, 8%) and appeared iso- to hypointense to brain on T1-weighted images, hypointense on T2-weighted images and showed uniform contrast enhancement.

  The differential diagnosis for meningeal-based lesions includes leukemia, lymphatic or carcinomatous masses and for type III.c. lesions choroid plexus papilloma have to be considered.
- *Type IV. Lesions of the hypothalamic-pituitary axis* These findings included **a:** infundibular thickening, IV.a. (8/38 patients, 21%), **b:** a partial or completely empty sella (14/38 patients, 37%), and **c:** lack of the posterior pituitary bright signs on T1-weighted MR images and hypothalamic mass lesions (4/38 patients, 10%).

  The differential diagnosis for infundibular thickening comprises sarcoidosis, infundibuloma, posttraumatic states and rare neoplasms; and for hypothalamic mass lesions, glioma, lymphoma, hamartoma and sarcoidosis.
- *Type V. Atrophy* (16/38 patients, 42%) Local or diffuse atrophy was a nonspecific finding with a multifactorial etiology.
- *Type VI. Therapy-related white matter changes* with/without contrast enhancement and specific high-signal intensity changes can be sen bilaterally within the deep gray matter as foci of calcification. These changes are not entirely specific, but are characteristic sequelae of radiation and chemotherapy damage to the CNS. They have to be considered in patients who were treated with these modalities for LCH at an early age (6/38 patients, 15%)

In one patient an astrocytoma grade III was found involving the pons and cerebellum emphasizing that neoplasms also must be included in the range of diagnoses.

Histopathological Findings

Biopsies of ill-defined cerebellar lesions (type I) revealed variable perivascular rarefaction, perivascular histiocytes and gliosis, including Bergman's gliosis, but no histiocytes of LCH phenotype were found.

The extraparenchymal lesions (type III) were fibro-

xanthomatous lesions also without Langerhans cell phenotype, but some changes were similar to the histology of juvenile xanthogranuloma. A few cells in some lesions were S100 positive but none had Birbeck granules nor were CD1a positive. These could be 'burnt out' lesions that once had the classical histiology of LCH. Typical LCH lesions with CD1a positivity and Birbeck granules on electron microscopy were found in biopsies from hypothalamic-pituitary lesions (type IV a., c.) and in one meningeal mass. Perhaps lesions of the hypothalamic/pituitary axis cause symptoms early in the course of disease and biopsy therefore 'catches' the LCH phenotype prior to transformation to the fibroxanithomatous state.

II. What Are the Open Questions?

1. *What is the etiology of CNS LCH?* Analogous to the uncertainty regarding the pathogenesis of LCH in general, the causes of CNS LCH remain a matter of speculation. What factors influence the evolution of the various types of CNS lesions (immunological imbalance, cytokine disequilibrium, viral infection)? Understanding what causes the histopathological entity of neuronal injury and astrocytosis (as seen in type I and II lesions) might allow the process to be arrested by therapeutic intervention.

   Our knowledge of neuronal damage in a variety of neurological disorders has been enhanced by a recent review article by Lipton and Rosenberg [3]. Glutamate and to a lesser extent, N-Methyl-D-Aspartate (NMDA), are the principal neuroexcitatory transmitters. Excessive activation of receptors for these amino acids allows 'excitotoxic' calcium influx into neurons causing neuronal injury and death. Many neurodegenerative diseases are thought to be mediated in this way. Subsequently, Lipton and Gendelman [4] have described the mechanism thought to cause neuronal damage and astrocytosis in the AIDS dementia syndrome. In this disease, the HIV-1 virus does not appear to invade neurons directly but stimulates brain macrophages and microglial cells through its viral glycoprotein coat (gp 120). This binds to the surface of macrophages causing them to secrete neurotoxins and cytokines followed by damage through the excitotoxic mechanism described above. Astrocytes are then involved in this interaction, producing additional neurotoxins, increasing the glutamate milieu by failure of uptake and inducing a block of neuron-dependent growth factors. It seems extremely likely that similar mechanisms are involved in CNS LCH given that LCH cells in other organs have features of activated macrophages i.e. excessive prostaglandin and cytokine production. The course of the disease could therefore potentially be arrested either by 'deactivation' of LCH cells before the cycle of neuronal damage has occurred or by preventing glutamate-receptor-mediated neurotoxicity once it has begun. In the former situation, therapy which is known to be effective in systemic disease might have a role, although this might have to be more CNS directed (see below). In the latter situation, a variety of pharmacological agents are at present under investigation.
2. *What is the incidence of CNS disease?* To answer this question, CNS screening tests would need to be performed on all newly diagnosed patients with LCH; but what tests should be performed and at what intervals? What diagnostic tests are indicated, reproducible, and justifiable in symptomatic patients? What tests are feasible to help elucidate the pathogenesis of LCH in the CNS?
3. *What therapeutic strategies can be offered to affected patients?* The serious and progressive nature of the parenchymal disease warrants the adoption of investigational therapeutic strategies since standard treatments (chemo- and radiotherapy) have been unavailing.

III. Recommendations

1. Diagnostic Evaluation

1.1. All LCH patients at initial diagnosis:

- Height, weight, pubertal status according to the Tanner scale
- Water deprivation test including urinary AVP to exclude partial diabetes insipidus (DI)
- Baseline hormone studies (T4, TSH, cortisol, FSH, LH, prolactin)
- Baseline age-appropriate tests of intellectual and motor development and behavioural tests (see below)
- MRI of the brain would be desirable as a baseline study. As MR is clearly superior to CT in the diagnosis of central nervous system disease in LCH, it is the noninvasive technique of choice and should be performed using state-of-the-art equipment to cover all aspects of possible pathologic findings. The administration of contrast media (Gd-DTPA) is mandatory.

1.2. Patients with documented CNS disease, i.e., patients with neurological symptoms and/or lesions on MRI

- Endocrine evaluation including water deprivation test and pituitary provocation tests (e.g. insulin tolerance, arginine or clonidine test) with measurement of cortisol, growth hormone, T4, TSH, and prolactin in all patients with DI, growth failure, precocious or delayed puberty or other evidence of hormonal dysfunction or in patients with lesions in the hypothalamic-pituitary axis.
- Serial MRI (with Gd-DTPA) should be performed at yearly intervals or more frequently in case of progression.

- Cerebrospinal fluid (CSF) should be obtained at diagnosis of CNS involvement and, in case of progressive disease. Studies should include nucleated cell count, cytospin identification and immunohistochemistry with markers of lymphocyte subsets and histiocytes (CD 1a, CD 68, lysozyme etc.) and chemical measurement of neopterin and lysozyme activity. Residual CSF should be frozen at −20°C for other studies as needed.
- Standardized, formal neuropsychometric and motor efficiency tests should include developmental tests* intelligence tests,** movement assessment,*** behavioural questionnaire**** and neurophysiological tests like conventional EEG, brain stem acoustic-evoked potentials (BAEP), visual evoked potentials (VEP), and somatosensory evoked potentials (SSEP).
- Brain biopsy to obtain tissue for histopathologic examination can rather easily be performed for type III and IV mass lesions often combined with a curative surgical approach. In type I or II parenchymal lesions, in particular in the brain stem, stereotactic biopsies are rarely indicated in the context of a history of LCH outside the CNS. The major problem in these cases is the small specimen size that can be obtained limited by the location, consistency and size of the lesion (usually less than 1–3 mm^3), and by the accuracy of the biopsy procedure itself. In fatal cases of LCH with evidence of brain disease, a carefully planned and executed autopsy should be done as soon as possible after death. Important tissue samples should be processed to maximize their usefulness.

2. Treatment

No general recommendations concerning treatment are possible at this point. The individual strategy is dependent on the type and the site of the lesions and the state of LCH outside the CNS.

Dural based (type IIIa.) lesions can be completely or partially resected if they exert a mass effect. The possible extent of the resection and the risk of the procedure depend on the site of the lesion and on its relationship to intracranial neural and vascular structures. Choroid plexus (type IIIc.) lesions can be excised even by an endoscopic technique, especially if the lesion leads to disturbances in CSF circulation. Sellar or suprasellar mass lesions in the hypothalamic-pituitary region (type IVa. and c.) can be approached microsurgically keeping in mind the major risk of endocrine impairment. Chemotherapy with agents of established efficacy in systemic LCH might be beneficial, although more CNS directed substances which are known to cross the blood brain barrier or intrathecal therapy should be preferred. Local irradiation might be another option when radical surgery is not possible.

Apart from these mass lesions, radiation therapy rarely seems indicated in CNS LCH. Its role in the treatment of DI remains a controversial issue. Considering the potential endocrine sequelae and the small chance of reversal of established DI, irradiation probably is not the method of choice in these cases. In those with parenchymal type I and II lesions the available data provide no evidence for a beneficial effect of radiotherapy. Further, the nature of these lesions is unclear; the few available histopathologic specimens revealed degenerative changes in which irradiation may even be harmful.

In summary, therapy in patients with type I and II lesions remains a dilemma. There is evidence that etoposide might have stabilized the course of the disease in some patients. Prednisone therapy also seems to have shown transient improvements in others. In different single cases cyclosporin, 2-chlorodeoxyadenosine, interferon alpha or intravenous immunoglobulins were tested without convincing effect. The number of patients reported is too small, however, and the clinical settings and the therapeutic approaches were so heterogenous that no definitive statements can be made at this point. In cases with a progressive course, experimental approaches with immunotherapy or with agents that prevent glutamate-receptor mediated neurotoxicity [3] are warranted.

3. Research directions

- *The LCH II protocol of the Histiocyte Society** includes mandatory minimal baseline tests and studies for all new LCH patients to be done at diagnosis and at 6-monthly intervals for the first 5 years and thereafter at yearly intervals. The *questionnaire* concerning CNS disease attached to the LCH II protocol should help to collect more information on the incidence of CNS disease and its variable presentations.
- *Brain biopsy or autopsy specimens and CSF samples* should be sent to Dr. Ron Jaffe, Department of Pathology, Pittsburgh Children's Hospital, 3705 Fifth Avenue, Pittsburgh, PA 15213. Telephone: 412 692-5657; Fax 412 692-6550. @mail: jaffek@chplink.chp.edu. Pathology consultation is available from R. Jaffe and

*Bayley Scales of Infant Development (range 2 months–2.5 years, Bayley 1993), Griffith Scales (range 0–7 years, Griffiths, 1967, 1970).
**Stanford-Binet Intelligence Scales (Terman and Merrill, 1961), Kaufman Assessment Battery for Children (range 2.5–12 years, Kaufman & Kaufman, 1983), Wechsler Intelligence Scales for Children (range 6–17 years, Wechsler, 1974).
***Movement Assessment Battery for Children (range 4–12 years, Henderson, 1985).
****Child Behaviour Check List (CBCL).

*Available from the LCH II Study Reference Center, Chairman Helmut Gadner, MD, St. Anna Children's Hospital, Kinderspitalgasse 6, 1090 Vienna, Austria. Telephone: +43-1-40170-476 Fax: +43-1-40170-430; @mail: gadner@ccri.univie.ac.at., grois@ccri.univie.ac.at

from B.E. Favara, Dept. of Health and Human Services, National Institutes of Health, Rocky Mountain Laboratories. 900 S. Second Street, Hamilton, MN 59840-2999. Fax/phone 406 363-0683; @mail blaise_favara@nih.gov.

• Brain tissue or CSF samples kept in the local institution shold be indicated on the questionnaire and thus be available for a coordinated research approach (e.g., measurement of cytokine levels or other neurotoxins or, viral studies).

ACKNOWLEDGMENT

The efforts and contributions of the participants of the panel G. Bernert, V. Broadbent, T. Czech, G. D'Angio, M. Egeler, B.E. Favara, G. Kannourakis, J. Kepes, G.H. Mostbeck, and D. Prayer are gratefully acknowledged.

THE WRITING COMMITTEE:

N. Grois, V. Broadbent, B.E. Favara, G. D'Angio

REFERENCES

1. Grois N, Barkovich AJ, Rosenau W, Abin AR: Central nervous system disease associated with Langerhans' cell histiocytosis. Am J Pediatr Hematol Oncol 15:245–254, 1993.
2. Grois N, Tsunematsu Y, Barkovich AJ, Favara BE: Central nervous system disease in Langerhans cell histiocytosis. Br J Cancer (Suppl. XXIII). 70:S24–S28, 1994.
3. Lipton SA, Rosenberg PA: Mechanisms of disease: Excitatory amino acids as a final common pathway for neurologic disorders. N Engl J Med 330:613–622, 1994.
4. Lipton SA, Gendelman HE: Seminars in medicine of the Beth Israel Hospital, Boston: Dermentia associated with the acquired immunodeficiency syndrome. N Engl J Med 332:934–940, 1995.